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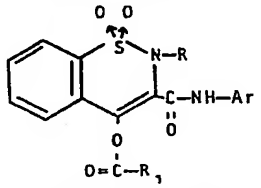
(54) **Derivatives of benzo-1,2-thiazine-1,1-dioxide, a process for their preparation and pharmaceutical compositions containing the same.**

(57) Esters of 4-hydroxy-2-alkyl-3-aminocarboyl-2H-1,2-thiazine-1,1-dioxide having formula (I)



(I)

where R stands for lower alkyl C_1-C_4;

R_1 stands for a linear or a branched alkyl bearing from 1 to 5 atoms of carbon and preferably ter-butyl;

Ar stands for an aromatic or heteroaromatic residue bearing from 1 to 3 etheroatoms such as O, S, N, and preferably the residues 2-pyridyl, 2-thiazolyl; and their addition salts with pharmaceutically acceptable acids are endowed with a therapeutic index higher the one of the parent, not esterified compounds.

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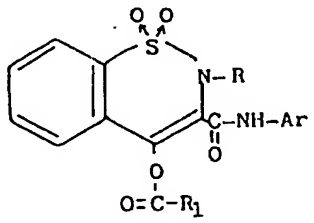
Derivatives of benzo-1,2-thiazine-1,1-dioxide, a process for their preparation and pharmaceutical compositions containing the same

The present invention refers to new derivatives of benzo-1,2-thiaxine-1,1-dioxide of general formula:



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where R stands for lower alkyl C_1–C_4;

R_1 stands for a linear or a branched alkyl bearing from 1 to 5 atoms of carbon and preferably ter-butyl;

Ar stands for an aromatic or heteroaromatic residue bearing from 1 to 3 etheroatoms such as O, S, N, and preferably the residues 2-pyridyl, 2-thiazolyl; and their addition salts with pharmaceutically acceptable acids.

Specific compounds included in the formula (I) are:

4-pivaloyloxy-2-methyl-2H-1,2-benzothiazine-3-/N-(2-pyridyl)-carboxamide/-1,1-dioxide; 4-pivaloiloxy-2-methyl-2H-1,2-benzothiazine-3-/N-(2-thiazolyl)-carboxamide/-1,1-dioxide.

In the U.S. Patent n. 3,591,584 a new class of compounds of the series of the 3-aminocarbonyl-1,2-benzothiazine-1,1-dioxide bearing heterocyclic residues at the amino-nitrogen has been reported for the first time.

Compounds of this kind are endowed with an analgesic and antiinflammatory activity, and some of them have been used in the therapy of arthro-rheumatic affections, in spite of presenting drawbacks especially due to the appearance of gastroenteric disorders in the treated patients; disorders, however, very common in other non-steroidic antiinflammatory compounds.

After our priority-filing of the present patent application (Italian Application n. 19486 A/82 of February 5, 1982) we have learned from the publication of the European Application n. 57059, filed on January 11, 1982, that also some esters of 4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-/N-(2-pyridyl)-carboxamide/-1,1-dioxide have been prepared and pharmacologically tested.

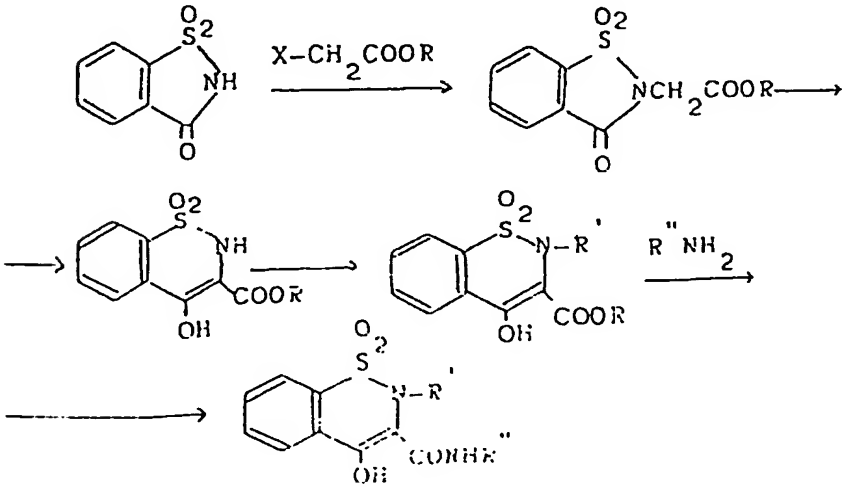
These new derivatives, nevertheless, do not present any real therapeutical advantage, since they possess, to a lower or a higher extent, the same characteristics as the starting compound; they simply turn out to be more suitable to the topic administration route.

It has instead been found, and it is the object of the present invention, that the esterifica

tion of the hydroxyl in position 4 in the structure in question with a particular kind of substituent allows to obtain a new compound with antiinflammatory activity that presents unforeseeable surprising advantages at therapeutic level.

It has in fact been established that only this particular new derivative corresponding to the formula (I), precisely obtained by means of esterification of the hydroxyl in 4-position with a ter-butyl radical, while it keeps substantially unaltered the antiinflammatory activity, it has a drastically reduced ulcerogenic activity, thus showing a therapeutic index 10.25 times higher than the one of the starting compound.

Various ways of synthesis followed to obtain the compounds described in the above-mentioned patents and other similar compounds are known from the prior art. One of these ways can be schematized as follows:

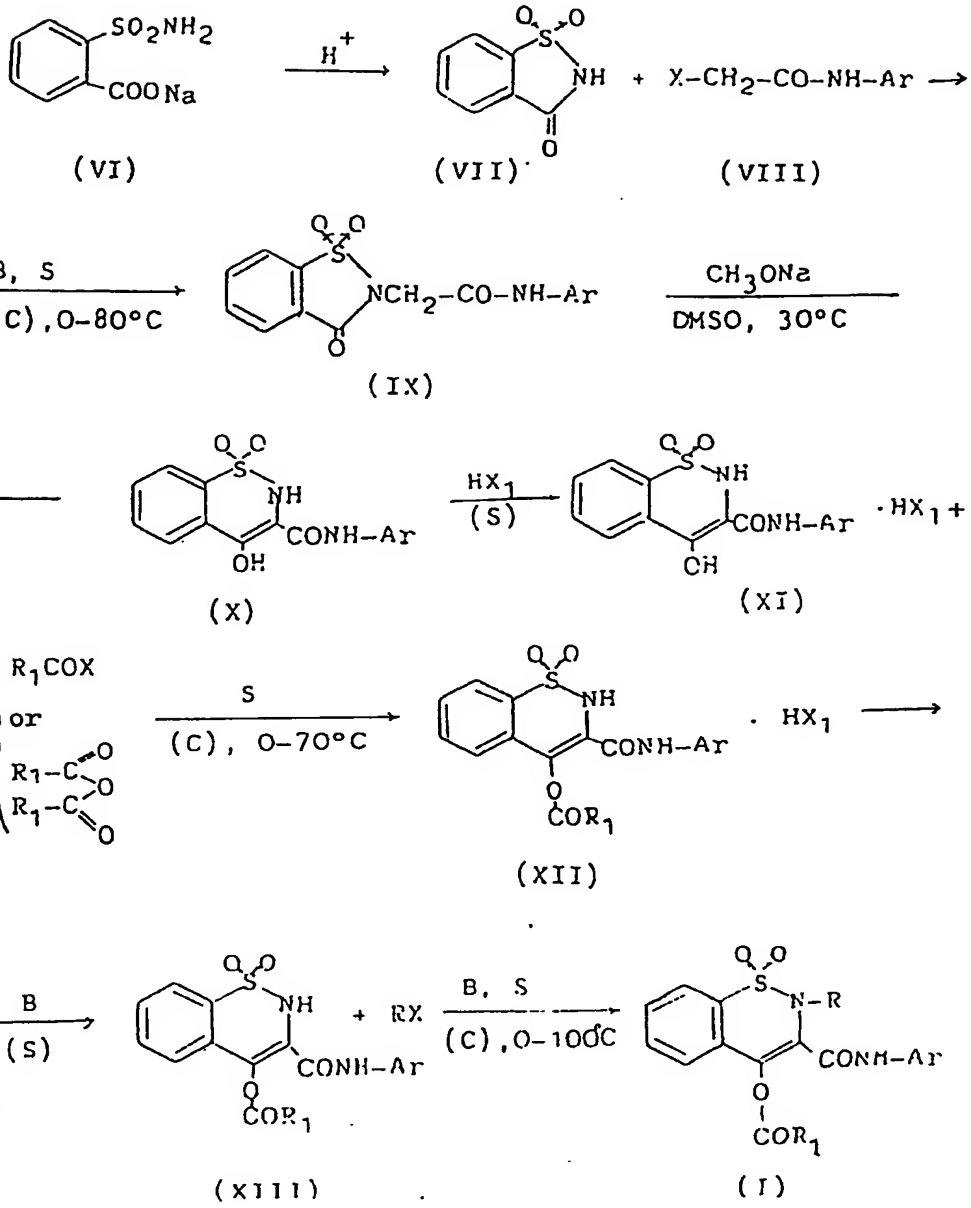


(where R and R' represent for example CH_3, whereas R'' represents for example H, alkyl, heteroaromatic residue); see U.S. pat. n. 3,591,584, 1971; Lombardino J.G. et al., J. Med. Chem. 14 (12), 1171, 1971.

Other alternative ways of synthesis described in patents and in the literature have not offered up to now particular advantages as compared to one indicated above.

It has now been found, and it is the object of the present invention, a new method to prepare the compounds of formula (I), which presents some interesting advantages.

According to the invention, the compounds (I) are obtained in conformity to the following reaction scheme, where R, R_1 and Ar have the meaning above specified for the formula (I), whereas X and X_1 are halogens, for example Cl or Br.


SO2NH2
COONa
H+
NH
X-CH2-CO-NH-Ar
(VI)
(VII)
(VIII)
B, S
(C), 0-80°C
NCH2-CO-NH-Ar
CH3ONa
DMSO, 30°C
(IX)
CONH-Ar
OH
HX1
(S)
·HX1+
(X)
(XI)
R1COX
or
R1-C
O
R1-C
O
S
(C), 0-70°C
COR1
·HX1
(XII)
B
(S)
+ RX
B, S
(C), 0-100°C
N-R
(XIII)
(I)

As it is evident, the main characteristic of the new process of synthesis of the invention is the fact of obtaining, from a pentaatomic derivative, an esaatomic ring already substituted in 3-position with the N-eterocyclic carboxamidic group. This involves a remarkable increase of the yields.

The general synthesis scheme is afterwards explained in a more detailed way.

The starting products (VI) and (VII) are commercially available or they can be prepared according to well-known methods.

As a matter of fact the compound (VII) can be obtained by neutralizing exactly with mineral acids the sodium salt (VI) dissolved in water, filtering, if necessary, the unreacted product, acidifying at pH 1-0 and filtering VII.

The intermediate VII is subsequently reacted with the compound X-CH_2CONMAr (VIII). This reagent is often commercially available, or its synthesis is well-known or it is easily obtainable according to well-known methods.

The reaction between the intermediate (VII) and the product (VIII) is carried out at temperatures ranging from 0 and 80°C, preferably from room temperature to the boiling temperature of the solvent that is used, and, if necessary, in the presence of a stoichiometric or catalytic quantity of a base and/or of an acidity acceptor (B), such as

aliphatic, aromatic or heterocyclic tertiary amines, hydroxydes or carbonates of alkali or earth-alkali metals, bicarbonate, acetates, hydrides, amides or alcoxides of alkali metals.

As solvents (S) all the ones that are commonly used, such as benzene, toluene, acetone, chloroform, 1,2-dichloro-ethane, dimethylformamide, water, methylene chloride, etc. can be used. It is also possible to carry out the reaction in double phase using water and one of the above-mentioned solvents. In some cases the solvent can be represented by the reagent itself used in excess.

The reaction may be carried out in presence of a catalyst (C), such as, for instance, a base like the ones described under "B", quaternary ammonium or phosphonium salts (especially in the double phase reactions), alkali iodides, or cuprous iodide, etc.

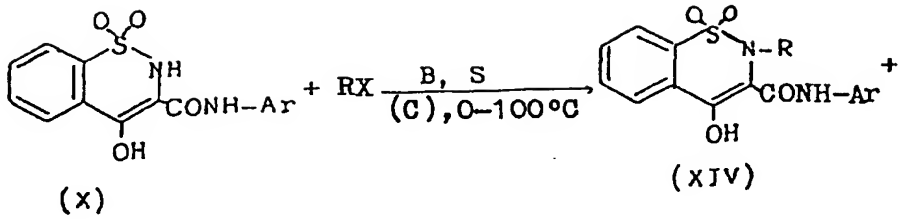
The expansion reaction of the thiazolic ring takes place by means of treatment of the intermediate (IX) with sodium methoxide in dimethylsulfoxide and by checking the exothermia of the reaction so that the temperature is not higher than 30-35°C.

The intermediate (X) thus obtained is transformed at a temperature that is lower than 5°C in one of its addition salts with mineral acids

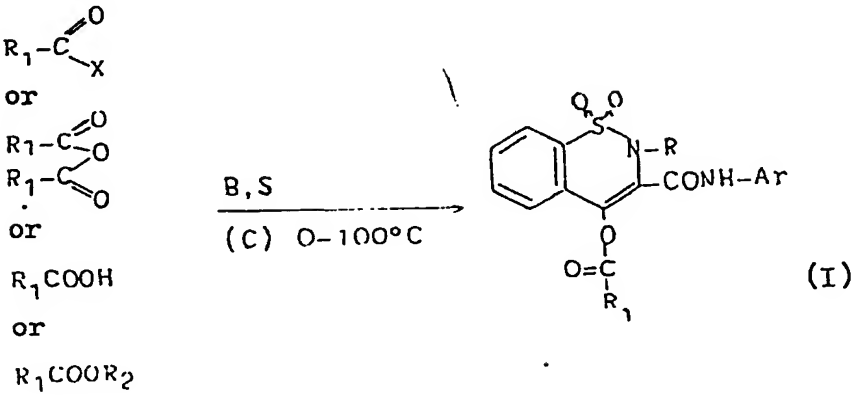
(HX_1) (preferably HCl), by addition of the acid (or of one of its solutions in solvent) to a solution of the intermediate (X) in a solvent that allows the precipitation of the previously formed salt. The intermediate (XI) is reacted with an acyl halide (R_1COX) or with the anhydride of a carboxylic acid $\overline{(R_1CO)_2O}$ in a solvent that can be chosen among the ones described before (S) (with the exception of water) and at temperatures ranging from 0 to 70°C. Also a catalyst (C) can be used, but more often this is superfluous. When the reaction is over the intermediate (XII) is isolated, and it is immediately transformed in the compound (XIII) by means of treatment with a stoichiometric quantity of a base (B) and/or in the presence of a solvent (S).

The intermediate (XIII) is finally reacted with the reagent RX in the presence of bases "B" in the absence or in the presence of solvents "S" and of catalysts "C", at temperatures ranging from 0 to 100°C, preferably at room temperature. For this reaction it is possible to use, as solvents, lower alcohols, from which it is possible to crystallize the final product (I).

The product of the general formula (I) can be prepared alternatively starting from the intermediate (X), by means of the following reactions:



(X) (XIV)

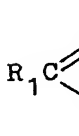
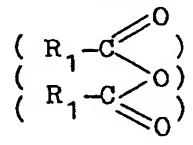


(I)

where R, R_1 and Ar have the meanings that have been previously defined for the general formula (I); R_2 stands for a lower alkyl; X stands for an halogen such as Cl, Br;

B, S, C have the meanings indicate above.

The intermediate (X) is reacted with RX in the presence of a base B, in the absence or in the presence of the solvent S and of the catalyst C, at temperatures ranging from 0 to 100°C, preferably at room temperature. The intermediate (XIV) that has been thus obtained is reacted with reagents such as

 (acyl halides) or  (carboxylic

acids anhydrides) or R_1-COOH (carboxylic acids) or R_1COOR_2 (esters of carboxylic acids), where R_2, R_1 and X have the same meanings they had before. The base B, the solvent S and the catalyst C are of the above-mentioned kind. Also acid catalysts are suitable (for example mineral acids such as sulphuric, phosphoric and hydrochloric acid). The reaction is carried out between 0-100°C, more often between room temperature and 60°C or at the boiling temperature of the solvent.

The final product of the general formula (I) is crystallized from solvents such as alcohols, ethers, methylene chloride, acetone etc., or from their mixtures.

The compounds of formula (I) thus obtained can moreover form addition salts with various pharmaceutically acceptable acids such as inorganic acids like hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, hydrobromic acid, or organic acids such as oxalic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, ascorbic acid.

These salts can be easily prepared in a well-known way, for example by adding an aequimolecular quantity or an excess of the acid to a solution of the compound of formula (I) in an organic solvent, such as methanol, ethanol, isopropanol, acetone and similar. The invention is ex-

plained in a more detailed way by the following examples, which, on the other hand, do not limitate it.

EXAMPLE 1

a) Preparation of intermediate (VII)

In a 500 ml beaker provided with magnetic stirrer 0.06 moles of intermediate VI, which are dissolved in about 200 ml of H_2O, are charged. When the dissolution is complete, 1 N hydrochloric acid is slowly added to exact neutrality (checking by means of indicator or pH-meter). The reaction mixture is now left under stirring for about 30' and the solid formed, if any, is filtered off.

The filtrate is acidified to pH 1-0.

The precipitated VII is filtered, washed with H_2O and dried in oven under vacuum. Yields vary from 65 to 90%. The product obtained is characterized by means of N.M.R., IR, U.V. spectra and of elementary analysis.

b) Preparation of the intermediate IX

In a 1-liter flash with stirrer, thermometer, reflux condenser, dropping funnel, external thermosthatic bath, 0.25 moles of intermediate (VII), 23 g of potassium carbonate, 200 ml of H_2O are charged. The reaction mixture is heated to 50°C for 25 minutes, then 8.5 g of tetrabutyl ammonium hydrogen sulphate are charged, thereafter the reaction mixture is stirred again for 18' at

50°C and 200 ml of benzene are charged and, under fast stirring, a solution of 0.3 moles of intermediate (VIII) dissolved in 250 ml of benzene, are slowly dropped in about 20'. The mixture is then refluxed for 70', cooled at room temperature, the phases are separated and the organic phase is washed with slightly acid H_2O, then with 1 N KOH and finally with water to neutrality. The benzenic phase is dried on K_2CO_3, thereafter the solvent is evaporated under reduced pressure. A crude product is obtained in a yield of 60-80% /intermediate IX/. The product is characterized, after crystallization from suitable solvents (for instance lower alcohols), by means of N.M.R., IR spectra and of elementary analysis.

c) Preparation of the intermediate XI

In a 500 ml flask provided with stirrer, thermometer, dropping funnel and external cooling bath 100 ml of dimethylsulphoxide (anhydrous), 0.2 moles of intermediate (IX) are charged and then, under fast stirring, a thick suspension of 21.5 g of sodium methoxide suspended in 100 ml of anhydrous dimethylsulphoxide is added in about one hour and in such a way as to not exceed 30°C of internal temperature.

When the addition is over, the reaction mixture is stirred again for 20' then acidified with 3 N HCl and extracted with $CHCl_3$. After drying, the $CHCl_3$ phase is evaporated, the residue /intermedia

te (X)/ is dissolved in ethanol and trasformed into the hydrochloride by addition of ethanolic HCl at 0°C. The hydrochloride /intermediate (XI)/ is obtained in a yield of 36-67% and it often does not call for crystallizzation. It can be characterized by means of its N.M.R., I.R. spectra and of elementary analysis.

d) Preparation of the intermediate (XIII)

In a 500 ml flask provided with stirrer, reflux condenser, external thermostatic bath 0.15 moles of intermediate (XI), 150 ml of 1,2-dichloroethane (anhydrous) are charged, the reaction mixture is stirred for 15' at room temperature, then cooled to 2-3°C and 0.16 moles of acyl chloride R_1COCl are charged in one portion.

The reaction mixture is thereafter stirred for 30' at 0-5°C allowing then the temperature to raise in about 90' to 20°C, and then heated in about 60' to 60-70°C. During this heating there is development of HCl continuing again for about 3 hours. At the end the reaction mixture is allowed to cool to room temperature and the product obtained is filtered /intermediate (XII)/. The intermediate (XII) is suspended in about 200 ml of H_2O and the suspension is then brought to pH = 7.3 with 10% KOH, keeping the temperature cool and under fast stirring. The suspension is stirred for about two hours and then the product obtained is filtered /intermediate (XIII)/ which can be re-crystallized from isopropa

nole and characterized by means of N.M.R., I.R. spectra and of elementary analysis. Yields are 78-92%.

e) Preparation of compound (I)

In a 1000 ml reactor provided with stirrer and thermometer, dropping funnel, 0.12 moles of intermediate (XIII), 400 ml of ethanol, 100 ml of water are charged. The reaction mixture is stirred for 15', then 120 ml of 1 N NaOH are added and the mixture is again stirred for 20' at room temperature; 0.38 moles of the alkyl halide RX are then charged, dropping in about 25'. The reaction is allowed to proceed for 18 hours at room temperature, the precipitate formed is filtered, washed with H_2O and finally dried. Yields are 65-90%. The product is characterized by means of N.M.R., I.R. spectra and of elementary analysis.

EXAMPLE 2

a) Preparation fof the intermediate (XIV) from the intermediate (X)

The reaction is carried out in completely analogous conditions to those described in point e) of Example 1.

Yields are 45-80%.

The product obtained having formula XIV is characterized by means of N.M.R., I.R. spectra and elementary analysis.

b) Preparation of final compound I

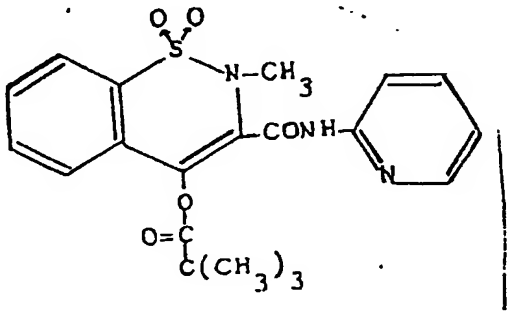
In a 1000 ml flask provided with stirrer, thermome

ter, reflux condenser, dropping funnel and external thermostatic bath, 0.133 moles of the intermediate (XIV), 300 ml of anhydrous 1,2-dichloroethane and 6.9 g of triethylamine are charged, the mixture is then heated to 50°C and a solution of acyl halide R_1COX (0.099 moles) diluted in 15 ml of dichloroethane is dropped (20'). A slight exothermia is noticed during the addition, at the end of which stirring is continued for 20' at 50°C. 6.8 g of triethylamine are then charged and stirring is continued again for 15' at 50°C, thereafter a solution of the acyl halide R_1COX (0.099 moles) in 15 ml of 1,2-dichloroethane is dropped in about 20'.

At the end of this second dropping, the temperature is still kept for 20' at 50°C, the reaction mixture is then left to cool at 30°C and filtered in order to remove the solid formed (triethylamine hydrochloride).

The filtrate is washed with 2x200 ml of H_2O, then with 2 x 200 ml of 0.5 N NaOH and finally with H_2O to neutrality. The solution in 1,2-dichloroethane is dried on Na_2SO_4, the solvent is then evaporated under vacuum till the obtaining of an oil which immediately solidifies and which is well pulped in ethyl ether. The suspension is filtered, washed with ethyl ether and the solid obtained, which does not require re-crystallization, is dried. Yields are 75-90%. The products are cha-

racterized by means of N.M.R., I.R. spectra and of elementary analysis. With the above described methods, the following products are obtained:



XV

4-Pivaloyloxy-2-methyl-2H-1,2-benzothiazine-3-[N-(2-pyridyl)-carboxamide]-1,1-dioxide.

White crystalline powder melting at 152-154°C.

^{1}H-NMR SPECTRUM at 60 MHz ($CDCl_3$)

(ppm, δ) = 9.0 (s, broad, mobile -NH-); 8.35-8.15 (m, 2H = H-5 and H-6 of the pyridine ring); 8.0-7.4 [m, 5H (4 aromatics + H-3 of the pyridine ring)]; 7.3-6.9 (m, 1H = H-4 of the pyridine ring); 3.05 (s, 3H = $-N-CH_3$); 1.4 [s, 9H = $-CH_3)_3$].

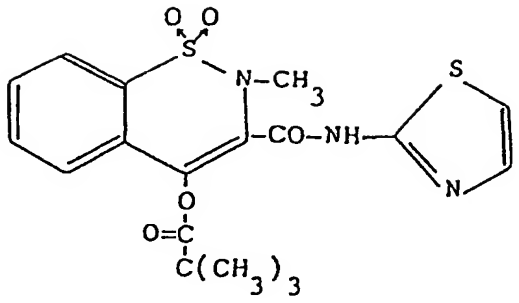
I.R. SPECTRUM (KBr) 3700-3150 cm^{-1} (broad); 2980 cm^{-1} (weak); 1760 cm^{-1}; 1680 cm^{-1}; 1530 cm^{-1}; 1435 cm^{-1}; 1350 cm^{-1}; 1300 cm^{-1}; 1090 cm^{-1}; 765 cm^{-1}.

ELEMENTARY ANALYSIS (C, H, N)

for $C_{20}H_{21}N_3O_5S$

calcd. % C = 57.82; H = 5.095; N = 10.11

found % C = 57.69; H = 5.087; N = 10.28.



(XVI)

4-Pivaloyloxy-2-methyl-2H-1,2-benzothiazine-3-[N-(2-thiazolyl)carboxamide]-1,1-dioxide.

White cream powder melting at 175-177°C.

^{1}H-NMR SPECTRUM at 60 MHz ($CDCl_3$)

(ppm, δ) = 11.1-9.9 (s, broad 1H mobile -NH-); 8.0-7.55 (m, 4H, aromatics); 7.5 and 7.0 (2 doublets of 1H each, J ≃ 4Hz = 2H thiazolics); 3.0 (s, 3H = $N-CH_3$); 1.4 (s, 9H = $-C(CH_3)_3$).

I.R. SPECTRUM

(KBr) 3680-3220 cm^{-1} (broad); 2980 cm^{-1} (weak) 1760 cm^{-1}; 1675 cm^{-1}; 1560 cm^{-1}; 1530 cm^{-1}; 1350 cm^{-1}; 1180 cm^{-1}; 760 cm^{-1}; 720 cm^{-1}.

ELEMENTARY ANALYSIS (C, H, N)

for $C_{18}H_{19}N_3O_5S$

calcd. % C = 51.29; H = 4.54; N = 9.97

found % C = 51.20; H = 4.46; N = 10.01.

The compounds object of the present invention have been characterized from the toxico-pharmacological point of view.

We report the results obtained with the compound 4-pivaloyloxy-3-methyl-2H-1,2-benzothiazine-3-[N-(2-

pyridyl)-carboxamide/-1,1-dioxide (CHF 1021) and 4-pivaloyloxy-2-methyl-2H-1,2-benzothiazine-3-/N-(2-thiazolyl)-carboxamide/-1,1-dioxide (CHF 1047).

In these studies the activity of compounds CHF 1021 and CHF 1047 has been compared with the one of piroxicam, one of the most active oxicam previously described, by now entered into the therapeutic practice, and with the one of two other esters: valerate and n-butyrrate of piroxicam (respectively CHF 1109 and CHF 1115).

Acute toxicity

The toxicity by single administration has been determined by oral route in male mice IVA:NMRI (SPF), fasting, with water ad libitum 18 hours before the experiment. The substances under exam were suspended in 1% carboxymethylcellulose. The results relative to the approximate LD_{50} values, determined by interpolation on Probitpaper, have been reported in Table I.

TABLE I

Compound	Approx. LD_{50} mg/kg
CHF 1021	1800
CHF 1047	>3000
CHF 1109	1100
CHF 1115	880
Piroxicam	345

Antiinflammatory activity in the test of plantar edema by carrageenin

Crl: CD(SD) male rats, weighing 170-205 g, previously subjected to an acclimation period of at least one week through housing in environment with costant thermohygrometric conditions and fasting with water ad libitum 18 hours before the start of the test, have been distributed "at random" in groups of 5-6 animals each (4 groups corresponding to 4 different dose levels for each compound). A group of control animals has been treated only with the vehicle.

The test has been performed in 2 subsequent experimental sessions:

1: piroxicam versus CHF 1021

2: piroxicam versus CHF 1047, CHF 1109 and CHF 1115.

The activity of the examined compounds, administered at different doses, by the oral route, has been valued by measuring the protection offered against the development of the oedema induced in the rat's paw by injecting (at a distance of one hour from the administration of the active principle) 0.1 ml of 1% carrageenin in physiologic solution in the subplantar aponeurosis of the rear right paw, according to the method of Winter (Winter C.A. et al., Proc. Soc. Exp. Biol. Med. 111, 544, 1962).

The volume of the treated paw has been measured

by means of a water-mercury pletismometer according to Leuce P., Arch. Int. Pharmacodyn. 136, 237, 1962) immediately before and at different times adter injection of the phlogogenic agent.

The results have been expressed as ED_{30} values calculated on the logarithmic regression straight lines of the percent dose/inhibition of the oedema development, in turn determined from the ratio between the mean AUC value (area under the curve representing the development of the paw volume in the time) in the different treated animals groups and the respective control groups.

Such results are shown in the Table II.

Gastrolesive activity

On the same animals on which the antiinflammatory activity has been determined, the gastrolesivity has been contemporaneously checked through macroscopic control of the gastric mucosa at a distance of 7 hours from the administration of the substance under examination.

For each treatment, the logarithmic regression straight lines of the dose - mm of ulceration (single values of each animal) have been determined.

On the ground of such lines the calculation of UD_3 values, that is a dose whereby a gastric lesion of the total extension of 3 mm is expected, has been performed.

The results obtained are shown in Figure II.

From the examination of the results, altogether represented in the table I and II the following considerations can be found. The compound CHF 1021 endowed with remarkable antiinflammatory activity, comparable to the one of the reference compound (piroxicam), surprisingly exhibits an ulcerogenic activity at least 10 times lower and an acute toxicity about 35% lower in comparison to the reference compound.

These properties of important antiinflammatory activity with considerable decrease of the ulcerogenic effect, constituting the most serious side-effect of non-steroidal antiinflammatory drugs, confer to the product in question a very remarkable therapeutic interest and they turn out so much unexpected if compared with the results obtained with the other analogous derivatives contemporaneously tested.

In fact:

- the compound CHF 1047 or pivalic ester of 4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-[N-(2-thiazolyl)-carboxamide]-1,1-dioxide (sudoxicam) presented a very low antiinflammatory activity.

His direct parent compound, sudoxicam, on the contrary, had explicated in analogous tests an antiinflammatory activity comparable to the one of piroxicam, our reference drug (Wiseman E.H., Lombardino J.G.: Oxicams - A novel family of Non-Steroidal Anti-inflammatory Drugs - Eur. J. Rheumatol. In-

flamm. 4(3), 280, 1981).

In this case, therefore, the esterification, at least with this kind of substituent, determined a very high loss of activity.

TABLE II: Data of the comparison tests between compound CHF 1021, CHF 1047, CHF 1109, CHF 1115 and piroxicam.
Values of ED_{30} (antiinflammatory activity) and of UD_3 (gastrolesive activity) are relative to the oral route and are expressed in /umol/kg

Exp. session	Compounds	Antiinflammatory activity ED_{30} (/umol/kg)	Gastrolesive activity UD_3 (/umol/kg)	Therapeutic index UD_3/ED_{30}	Relative therapeutic index*
I	piroxicam	7.8	9.3	1.2	1
	CHF 1021	7.9	97.2	12.3	10.25
II	piroxicam	9.7	27.2	2.8	1
	CHF 1047	≃762	121.2	0.2	0.07
	CHF 1109	7.0	28.2	4.0	1.43
	CHF 1115	5.7	23.9	4.2	1.50

* Therapeutic index relative to piroxicam considered as 1.

- Compounds CHF 1109 and 1115 although having a good antiinflammatory activity, analogous or also slightly higher than the one of the parent compound, do not show an improvement of tolerability (on the contrary CHF 1115, n-butirryl ester of piroxicam, is slightly more ulcerogenic with a potency ratio of 0.88 to 1), whereby their relative therapeutic index is a little higher than the one of the reference compound: respectively 1.43 and 1.50.

Other pharmacological characteristics of CHF 1021

In other tests of direct comparison between piroxicam and CHF 1021, the latter confirmed its antiinflammatory activity, along with a good analgesic and antipiretic activity. The potency ratios (ratios between ED_{50} values) calculated on molar basis point out that CHF 1021 is 1.52-0.49-0.72-0.71 times as active as the reference compound on the plantar oedema by nystatin in the rat, on the erythema by U.V. in the guinea pig, on the writhing test by phenylquinone in the mouse and on the fever by beer's yeast in the reat. The two compounds are almost equally active on the arthritis by adjuvant in the rat.

Preliminar clinical data allowed to point out that CHF 1021 confirms to be a valid antiinflammatory drug practically equally active in comparison with piroxicam but with a clearly lower

incidence of side effects (about 1/3 than that of the reference drug).

The present invention refers moreover to pharmaceutical compositions containing as the active principle a compound of formula (I), as defined above, as such or as a pharmaceutically acceptable salt, in association with at least one pharmaceutically acceptable excipient.

The compositions can be administered orally, parenterally or topically, in the form respectively of capsules, tablets or similar compositions, suppositories, vials, cream or gel.

For the preparation of the pharmaceutical formulation for the oral administration in unitary dose, the active principle can be mixed with a solid powdered, excipient, such as for instance lactose, saccharose, sorbitol, mannitol, potato or cereal or maize starch, or amylopectin, a derivative of cellulose or gelatin, and it can moreover contain lubricant such as talcum, polyethylenglycole or silica, magnesium or calcium stearate.

The tablets can be variously coated according to well-known methods in the pharmaceutical art.

Capsules of hard gelatin can contain granulates of the active principle together with solid powdered excipients, such as lactose, saccharose, sorbitol, mannitol, starches (of the kind indicated above), cellulose or gelatin derivatives, and they may also contain stearic acid or magnesium stearate or

talcum.

Unitary doses for rectal administration may be in the form of suppositories containing the active principle in association with a neutral fat base (example glycerides of fat acids) or with water-soluble or autoemulsifiable excipients (example polyethylenglycole mixtures).

For injectable compositions for parenteral administration, the excipients can be a pharmaceutically acceptable sterile liquid such as water or an aqueous solution of polyvinylpyrrolydone or, again, an oil such as, for instance, peanut-oil and, if necessary a stabilizing agent and/or a buffer.

The active principle can be dissolved in the liquid and sterilized on filter before being put in a vial or it can be suitably lyophilized; in this case vials of liquid for injections will be added in the packagings in order to reconstitute the solution before use.

In the case both of the composition in suppositories and in vials a local anaesthetic, if necessary, can be added to the excipients.

The unitary dose for the formulations described above can vary from 10 to 200 mg of active principle and the daily administration will be preferably single.

For the preparation of formulations for topic use, fat-base excipients, such as vaseline, pa

raffin oil, lanoline etc. can be used, as well as autoemulsifiable excipients such as alcohols, fats, polyethylenglycoles, ethers or esters of fat acids or other tensides emulsified in water in the case of unguents, ointments and creams. On the contrary, in the case of preparations of gel of hydrophylic colloids, polymers of different kinds will be used, such as carboxyvynylpolymers, sodium carboxymethyl cellulose, methylcellulose, Methocel gelatinized in water, ethanol, propylenglycol, glycerole, polyethylenglycols, etc.

The topic preparations indicated above can be advantageously added to suitable antibacterial agents, such as parabens, phenol derivatives quaternary ammonium salts, etc.

The concentration of the active principle can vary in these compositions from 1 to 10%.

We report some formulations as exemplification.

Formulation in hard gelatin capsules for oral administraions

Composition at three different dosages:

CHF 1021	mg	30	40	60
Microcrystalline cellulose (Avicel®)	"	37.5	35	30
Dihydrated dibasic calcium phosphate (Encompress®)	"	105	98	84
Talcum	"	6.54	6.1	5.23
Magnesium stearate	"	0.96	0.9	0.77

For the preparation of N. 5000 capsules, with the components that are proportionally present in the above-defined quantities in relation to the dosage of the active principle, the following operations are carried out.

The raw materials are sieved, they are loaded in a powder mixer, the mixture is homogenized. The homogeneous mixture thus obtained is divided into capsules or opercula of hard gelatin by means of operculum-machine.

The weight of unitary mixture for capsule is of 180 mg.

Formulations in suppositories for rectal administration

Composition at three different dosages:

CHF 1021	mg	30	60	100
Semi-synthetic glycerides (Witepol®)	"	1570	1540	1500

For the preparation of N. 5000 suppositories, with the components that are proportionally present in the above-defined quantities in relation to the dosage of the active principle, the following operations are carried out.

The mass of excipient is melted at 40°C. The active principle is incorporated in the melted mass operating with a suitable mechanic dispersant. The mass is cooled at 36°C and it is poured, keeping the suppository mass under stirring, in PVC or aluminium valves having the unitary volume of 1.8 ml.

The weight of the suppository mass distributed for each valve is of 1.6 g. It is let solidify and the containers are suitably sealed.

Formulations in cream for topic administration

Composition at two different dosages of a cream of oil-water emulsion kind:

CHF 1021	g	2	5
Octyldodecanole (Eutanol G®)	"	7	7
Liquid triglyceride C_8 (Miritol 218®)	"	3	3
Polioxyethylene cetostearyl alcohol (Emulgin B_1/B_2®)	"	2	2
Propylenic glycole	"	5	5
Carboxyvinylpolymer (Carbopol 940®)	"	1	1
Fenocombin®	"	1	1
Sodium hydroxide	Q.S.at pH 5.5	Q.S.at pH 5.5	
Purified water	" " g 100	" " g 100	

For the preparation of kg 5 of cream, with the components that are proportionally present in the above-defined quantities in relation to the concentration of the active principle, the following operations are carried out.

The carboxyvinylpolymer is dispersed in water (20% of the quantity necessary to the preparation of the lot) and it is neutralized with soda in the quantity required to obtain a pH 5.5. The components and the fat phase are united in

a suitable foundry and they are melted at the temperature of 70°C.

The active principle CHF 1021 is dispersed in glycol and water (10% of the quantity necessary to the preparation of the lot), the preservative is dissolved in the residual quantity of water and the solution is taken to 80°C.

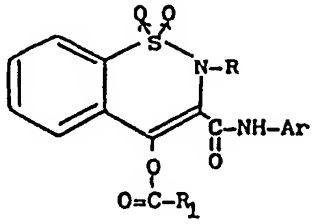
The aqueous phase is poured in the fat phase carrying out the homogenization with suitable emulsifier. It is cooled to 40°C and the emulsion is added with the hydroglycolic suspension of the active principle. The emulsion is finally stabilized with the gel of CV Polymer added and dispersed by means of suitable mechanic stirrer.

pH Is checked and adjusted at 5.5.

Cream is distributed in flexible aluminium tubes or in other suitable packaging material for preparations for topic use.

Claims:

1. Compounds of general formula (I)



(I)

where R stands for a lower alkyl C_1-C_4;
R_1 stands for a linear or a branched alkyl bearing from 1 to 5 atoms of carbon atoms;
Ar stands for an aromatic or heteroaromatic mono- or bicyclic residue bearing from 1 to 3 heteroatoms such as O, S, N and preferably the residues 2-pyridyl, 2-thiazolyl.

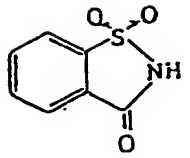
2. 4-Pivaloyloxy-2-methyl-2H-1,2-benzothiazine-3-/N-(2-pyridyl)-carboxamide/-1,1-dioxide.

3. 4-Pivaloyloxy-2-methyl-2H-1,2-benzothiazine-3-/N-(2-thiazolyl)-carboxamide/-1,1-dioxide.

4. Process for the preparation of the compounds of claim 1, characterized in that:
a N-arylchloroacetamide (VIII)

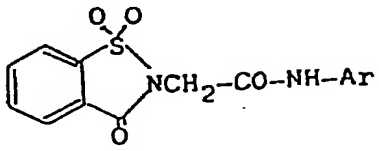
$$X\text{-}CH_2\text{-}CONH\text{-}Ar \qquad (VIII)$$

where X means a halogen atom and Ar has the meaning indicated in claim 1 is reacted with the intermediate (VII) of formula



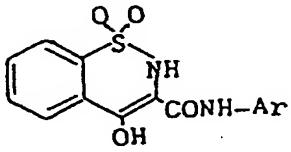
(VII)

to obtain a compound of the general formula (IX)



(IX)

where Ar has the above indicated meaning and in a single step compound (IX) turns into the benzothiazinic derivative (X) of formula:



(X)

where Ar has the above indicated meaning and compound (X), as such or in the form of one of its addition salts, is esterified at the hydroxyl group by reaction with an acylating agent and it is finally alkylated at the nitrogen atom in 2.

5. Process according to claim 4, characterized in that the transformation of IX in X takes place in the presence of sodium methoxide and dimethylsulfoxide at temperature no higher than 30-35°C.

6. Process according to claim 4, characteri

zed in that the esterifiation reaction can take place in the absence or in the presence of solvents, bases and catalysts and at temperatures ranging from 0 to 100°C, preferably at room temperature.

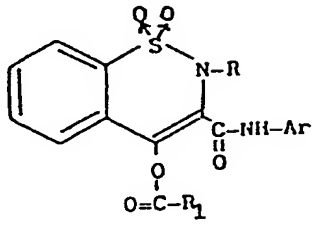
7. Pharmaceutical formulation at analgesic and antirheumatic activity, containing as active principle a compound according to claim 1, or one of one of its pharmaceutically acceptable salts.

8. Pharmaceutical formulation according to claim 7 for oral, rectal or parenteral administration in the form of capsules, tablets coated if necessary, suppositories or vials, containing from 10 to 200 mg of active principle per unit dose.

9. Pharmaceutical composition according to claim 7, for topic administration, in the form of cream or gel, containing the active principle in concentration from 1 to 10%.

Claims:

1. Process for the preparation of compounds of general formula (I)



(I)

where R stands for a lower alkyl C_1–C_4;

R_1 stands for a linear or a branched alkyl bearing from 1 to 5 atoms of carbon atoms;

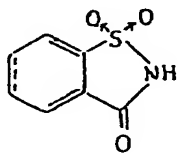
Ar stands for an aromatic or heteroaromatic mono- or bicyclic residue bearing from 1 to 3 heteroatoms such as O, S, N and preferably the residues 2-pyridyl, 2-thiazolyl,

characterized in that:

a N-arylchloroacetamide (VIII)

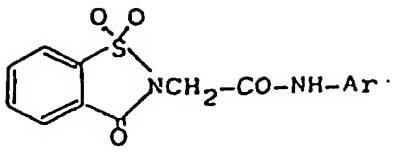
$$X\text{–}CH_2\text{–}CONH\text{–}Ar \qquad (VIII)$$

where X means a halogen atom and Ar has the above indicated meaning, is reacted with the intermediate (VII) of formula



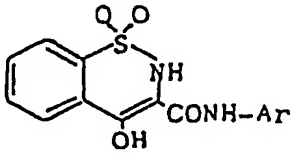
(VII)

to obtain a compound of the general formula (IX)



(IX)

where Ar has the above indicated meaning and in a single step compound (IX) turns into the benzothiazinic derivative (X) of formula:



(X)

where Ar has the above indicated meaning, and compound (X), as such or in the form of one of its addition salts, is esterified at the hydroxyl group by reaction with an acylating agent and it is finally alkylated at the nitrogen atom in 2.

2. Process according to claim 1, characterized in that the transformation of IX in X takes place in the presence of sodium methoxide and dimethylsulfoxide at temperature no higher than 30-35°C.

3. Process according to claim 1, characterized in that the esterifiation reaction can take place in the absence or in the presence of solvents, bases and catalysts and at temperatures ranging from 0 to 100°C, preferably at room temperature.

4. Process according to claims 1-3, characterized in that R is methyl, R_1 is t.butyl and Ar is 2-pyridyl.

5. Process according to claims 1-3, characterized in that R is methyl, R_1 is t.butyl and Ar is 2-thiazolyl.

European Patent Office

EUROPEAN SEARCH REPORT

0085866
Application number

EP 83 10 0504

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int Cl ³)
X	US-A-4 309 427 (J.G. LOMBARDINO) * Whole document, especially example 2 *	1,4-9	C 07 D 417/12 A 61 K 31/54 // C 07 D 275/06

TECHNICAL FIELDS SEARCHED (Int. Cl. ³)

C 07 D 417/00
C 07 D 279/00
A 61 K 31/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	26-04-1983	CHOULY J.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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